ATTACHMENT B

REMARKS

By this amendment, Applicants have amended the claims in a manner which overcomes all prior rejections and now places this application in condition for allowance. In particular, the main claims are now directed to the monoclonal antibody which recognizes the binding region identified as CNA19 which is the region at amino acids 151-318 of the collagen binding protein CNA, such as disclosed, e.g., at page 15-16 and in the examples of the original specification. In addition, the ability of the antibody to displace *S. aureus* from collagen, as is disclosed in the specification and examples, is also incorporated in the claims, and other minor changes have been made to Claims 29 and 34 to make these claims proper as well. Applicants submit that in light of the Amendments and arguments as set forth herein, the present application has been placed in condition for allowance for the reasons as set forth below.

In the Official Action, the Examiner objected to Claim 34 which inadvertently was directed to *S. aureus* when it was supposed to be directed to *S.* epidermidis. Applicants have now corrected this inadvertent error. In addition, the Examiner had a minor objection to the language of the claims, namely to the term "CNA19" which the Examiner indicated was used "without definition" in the claims. Indeed, the term CNA19 is not only well defined in the application, it is actually defined in the claims because the region to which it refers, namely amino acids 151-318 of the collagen binding protein of *S. aureus*, was included in the claims. In any event, Applicants have attempted to overcome the objection by removing reference to "CNA19" in the claims.

In the Official Action, the Examiner rejected the claims on the grounds of obviousness-type double patenting rejections with regard to co-pending serial number 09/813,820 and U.S. Pat. No. 6,288,214. In addition, the Examiner rejected the claims under 35 U.S.C. §103(a) and 102(e) on the basis on the basis of U.S. Pat. No. 6,288,214, and rejected the claims under 35 U.S.C. §102(b) as being anticipated by WO 97/43314, the PCT equivalent to the application that issued as U.S. Pat. No. 6,288,214.. The cited application, 09/813,820 is in fact a pending divisional application of the application which issued as U.S. Pat. No. 6,288,214, so all of these references have equivalent disclosures, namely they relate to the full collagen binding protein and antibodies thereto, and to an antibody raised to the M55 region of the collagen binding protein, and do not disclose or suggest the present monoclonal antibody for CNA19, the region located at amino acids 151-318 of the collagen binding protein. This rejection, insofar as applied to the claims as amended, is respectfully traversed for the reasons as stated below and in the accompanying Declaration of Dr. Joseph M. Patti, Ph.D.

In short, the prior applications and patent references cited by the Examiner relate to a collagen biding protein identified as CNA, and to particular regions of the CNA collagen binding domain such as M55 which is located at amino acids 30-531 of the full length collagen binding protein, as well as to antibodies generated thereto. However, these patent references do not disclose monoclonal antibodies that are specific for the CNA19 region, nor do they disclose any such antibodies which are cross-reactive and which have the unexpected and remarkable property of being able to displace bacteria that are already adhered to collagen. As shown in the attached Declaration of Dr. Joseph M. Patti, Ph.D., the present claimed invention was highly unexpected and

beneficial in that it provides antibodies that are cross-reactive to *S. epidermidis* in a manner not possible prior to the present invention so as to allow further protection from infection, and that are capable of displacing *S. aureus* when bound to an extracellular matrix protein such as collagen. As Applicants have previously indicated, the cross-reactivity of the CNA19 antibody to *S. epidermidis* was very unexpected since there are major differences between *S. aureus* and *S. epidermidis,* in terms of bacterial type and structure, and thus it was unexpected that a monoclonal antibody recognizing CNA19 of *S. aureus* would also recognize epitopes from *S. epidermidis*.

Moreover, the ability of the monoclonal antibody to CNA19 to actually displace collagen from the extracellular matrix protein and in effect detach *S. aureus* cells adhering to collagen was one of the most remarkable and unexpected properties observed in the study of this antibody. Previously, no such displacing behavior had been observed, and it had not previously known or expected that any particular antibodies to extracellular matrix proteins (or MSCRAMM®s) could actually act to displace bacteria that was already adhering to the collagen or other MSCRAMM®s on the cells. Indeed, not only was this displacing behavior shown in our experiments (such as disclosed, e.g., in Example 2 of the specification), it was also the case that bacteria that had adhered to a collagen substrate for up to at least 5 hours could still be displaced by the monoclonal antibodies to CNA19 in accordance with the present invention. This unexpected beneficial property will make the monoclonal antibodies of the present invention particularly effective in cases wherein a prior infection is present. See Patti Dec., ¶ 3.

Accordingly, the prior applications and patent references relating to the full CNA protein (such as U.S. Pat. No. 6,288,214 and the related applications) did not disclose or suggest any monoclonal antibodies "capable of displacing S. aureus to collagen", much less one that is capable of specifically binding to CNA19, nor did they disclose any cross-reactive monoclonal antibodies, much less one that is capable of specifically binding to CNA19. Moreover, the Examiner's comments that the prior antibodies to the full CNA protein and to the M55 region (SEQ ID NO:6 of U.S. Pat. No. 6,288,214) would necessarily also recognize the CNA19 region at amino acids 151-318 of the CNA protein, is not true, particularly in light of the fact that monoclonal antibodies are based on a very specific epitope within a given region, and thus it is extremely unlikely that a monoclonal antibody raised against a far greater region would be able to recognize the specific epitope or epitope of the monoclonal antibody to the specific region. See Patti Dec., ¶ 5. It is thus clearly **not** the case that the prior antibodies to the full CNA protein or to the M55 region (amino acids 30-531) would specifically recognize the CNA19 region, and our prior references did not disclose or suggest the present monoclonal antibody to CNA19 which has the unexpected beneficial features as set forth above.

Finally, as shown in the attached Declaration, it is also the case that no one can produce a monoclonal antibody to any particular region or epitope with any reasonable certainty that such a monoclonal antibody will be successful in achieving protection against infection. Accordingly, the fact that the present monoclonal antibody to CNA19 has the beneficial properties recited above, including displacing activity and cross-reactivity, is totally unexpected since it has been very hard to predict with any certainty

which monoclonal antibodies to which proteins, or fragments or domains, will result in antibodies capable of afforded protection against infection. See Patti Dec., ¶¶6-8.

Accordingly, before one actually goes forward with attempting to prepare a monoclonal antibody based on any particular surface protein, there are no guarantees that such an antibody can be adequately produced, much less with any certainty that the resulting monoclonal antibody will have success in achieving protection against infection. It is also uncertain as to which particular epitope of any particular protein will result in a protective monoclonal antibody. It was thus an unexpected result that monoclonal antibodies raised against the CNA19 by the present inventive group provided the properties as set forth above and gave excellent results in achieving protection well beyond that which would have been expected by one of ordinary skill in the art.

Applicants thus submit that the patent references including U.S. Pat. No. 6,288,214 and its related applications clearly do not disclose or suggest the present monoclonal antibody to CNA19 and thus do not anticipate or make obvious Applicants' present claims. The rejections on the basis of these references are thus respectfully traversed and should be withdrawn.

In the Official Action, the Examiner also rejected the claims under 35 U.S.C. §102(b) as being anticipated by the 1995 Patti et al. article and the 1992 Patti et al. articles which are directed to earlier work of this inventive entity dealing with the full length collagen binding protein CNA of *S. aureus*. As such, neither of these references discloses or suggest the presently claimed monoclonal antibodies because they once again relate to antibodies to the full CNA protein that are entirely different from the

monoclonal antibodies of the present invention which specifically recognize the CNA19 region, which are cross-reactive and which have the ability to displace *S. aureus* from collagen, a property that was not shown or described in the cited Patti articles. Accordingly, for the reasons as stated above and in the attached Declaration of Dr. Joseph M. Patti, it is clear that the two cited Patti et al. articles, either singly or in combination, do not disclose or suggest the presently claimed invention of a monoclonal antibody capable of recognizing the CNA19 region. As such, the Examiner's rejection on the basis of these references is respectfully traversed and should be withdrawn.

Finally, in the Official Action, the Examiner rejected Claims 1, 9, 10 and 23 under 35 U.S.C. §102(b) as anticipated by the Schiotz reference and Claims 1, 9 and 10 under 35 U.S.C. § 102(b) as anticipated by the Espersen reference. These rejections, insofar as applied to the claims as amended, are respectfully traversed. In particular, the Examiner appears to have simply assumed that these references inherently disclosed the CNA binding protein and simply argued that since the references discussed some cross-reactivity that antibodies to CNA must have been present, which is untrue as shown below.

In particular, as is pointed out in the attached Declaration, there is nothing in the Schiotz and Espersen references that have anything to do with the present invention, namely monoclonal antibodies to the CNA19 region of the collagen binding protein. In the first place, there is simply no disclosure in Schiotz or Espersen of any antibodies to the CNA protein or to regions therein, nor is there any disclosure to monoclonal antibodies or to antibodies capable of displacing an extracellular matrix protein of *S. aureus* from collagen.

Moreover, the Examiner's arguments appear to be based on the assertion that the Schiotz reference disclosed a cross-reactive antibody that "was generated against sonicated antigens from S. aureus that includes CNA-19 region." (Official Action at page 11, last paragraph) and that Espersen disclosed an antibody which "recognizes antigens of all S. aureus strains that includes CNA19 region." See the Official Action at page 12, middle paragraph. It is apparent that the Examiner assumed that the CNA protein is somehow inherent in each and every *S. aureus* strain and for that reason alone she concludes it must be present in the strains utilized in these references. Not only is the Examiner's position untrue, the opposite is the case and there are in fact many strains of S. aureus which **do not even possess the CNA gene and protein.** This is shown for example in the enclosed Abstract (attached as Exhibit 2) from Smeltzer et al., Poult. Sci. 79(7):1042-9 (July 2000) which states that "To date, only one collagen-binding adhesin (Cna) has been identified, **and the gene encoding this adhesin (cna) is not present in most S. aureus strains**." (Emphasis added). See Patti Dec., ¶¶ 9-10.

In short, neither Schiotz nor Espersen disclose, inherently or otherwise, any CNA binding proteins or regions, nor antibodies thereto, much less the specific monoclonal antibody directed to CNA19 in accordance with the present invention. Accordingly, the Examiner's rejections on the basis of these references, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

In light of the amendments and arguments as set forth above, as well as the Declaration appended hereto, Applicants submit that the present application overcomes all prior rejections and has been placed in condition for allowance. Such action is earnestly solicited.

END OF REMARKS